REMARKS

Present Claims 5- 11 relate to methods for crystallizing N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, comprising:

crystallizing N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester from a solution comprising N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester and a solvent, to obtain crystals of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester which exhibit at least the following diffraction peaks as measured by x-ray diffraction, 2θ CuKα:

a peak at 6.0°;

a peak at 24.8°;

a peak at 8.2°; and

a peak at 16.5°,

wherein said solvent is selected from the group consisting of water and mixtures of water and a lower alcohol,

wherein said crystallization is carried out such that the temperature of said solution is maintained above 30 °C until onset of nucleation of said N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester.

Present Claims 12-15 relate to methods for crystallizing N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, comprising:

crystallizing N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester from a solution comprising N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester and a solvent, to obtain crystals of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-

phenylalanine methyl ester which exhibit at least the following diffraction peaks as measured by x-ray diffraction, 2θ CuKα:

a peak at 6.0°;

a peak at 24.8°;

a peak at 8.2°; and

a peak at 16.5°,

wherein said solvent is selected from the group consisting of water and mixtures of water and a lower alcohol,

wherein said crystallization is carried out in the presence of seed crystals of said N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester, and

wherein said seed crystals of said N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester exhibit at least the following diffraction peaks as measured by x-ray diffraction, 2θ CuKα:

a peak at 6.0°;

a peak at 24.8°;

a peak at 8.2°; and

a peak at 16.5°.

The inventors have surprisingly found that the presently claimed methods yield an especially stable form of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester (hereinafter referred to as "neotame"), which is referred to as the A-type crystal form. At the outset, it must be emphasized that the present inventors were the first to find that A-type crystal exhibits excellent stability (see, *e.g.*, page 4, Table 1 and the surrounding description thereof, of the instant specification) as compared to the other polymorphic forms

of neotame such as the B-type, G-type, and the like. The excellent stability of the A-type crystals is, in turn, very useful from the commercial point of view (see, *e.g.*, paragraph bridging pages 1 and 2, of the instant specification). Moreover, as explained in the specification:

> As has been described above, a process for ***stably*** preparing ***A-type crystals excellent in stability***, of N-(3, 3-dimethylbutyl)-APM at a low cost, has not yet been established in the existing state of art.
>
> Therefore, it is an object of the present invention to, provide a process for ***stably and conveniently*** preparing highly stable A-type crystals of N-(3, 3-dimethylbutyl)-APM, which is a high intensity sweetener.
>
> With a view to attaining the above-described object, the present inventors have carried out an extensive and intensive investigation. As a result, it has been found that, upon crystallization of N-(3, 3-dimethylbutyl)-APM from a crystallization solvent consisting of water singly or a mixed solvent of water/alcohol, ***A-type crystals*** can be obtained stably as wet crystals ***by controlling the nucleation temperature***, and the type of the crystals to be precipitated can be controlled to be A-type by ***using A-type crystals as seed crystals***; and that dry A-type crystals can be obtained by drying these A-type crystals to have a water content of 3 to 6 wt.% (inclusive of the water of crystallization). Based on these findings, the present invention has been completed. It should be noted that the term "controlling the nucleation temperature" as used herein means "controlling so as to generate nucleation at 30°C or greater".
>
> Accordingly, the present invention relates, in a first aspect, to a crystallization method of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester crystals exhibiting the specific peaks of diffracted X-rays at angles of diffraction (2θ, CuKα rays) of at least 6.0°, 24.8°, 8.2° and 16.5°, which comprises using water alone or a mixture of water and a lower alcohol as the crystallization solvent and ***controlling the nucleation temperature at 30 °C or greater***, and in a second aspect, to a crystallization method of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester crystals, which comprises using water alone or a mixture of water and a lower

> alcohol as the crystallization solvent and ***using, as the seed crystals***, N-[N- (3, 3-dimethylbutyl) -L-α-aspartyl]-L-phenylalanine methyl ester crystals exhibiting the specific peaks of diffracted X-rays at angles of diffraction (2θ, CuKα rays) of at least 6.0°, 24.8°, 8.2° and 16.5°, whereby the same type of crystals as the seed crystals are preferentially precipitated.

Present Specification, page 4, line 15 from the bottom, to page 6, line 2, emphasis added.

The cited references contain no disclosure or suggestion of the presently claimed methods or the advantages afforded thereby. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 1 and 2 under 35 U.S.C. § 102(b) or, in the alternative, under 35 U.S.C. § 103(a) in view of U.S. Patent No. 5,510, 508 (Claude et al) and the rejection of Claims 3 and 4 under 35 U.S.C. § 103(a) in view of Claude et al and further in view of WO 93/02101 (Tosoh) are respectfully traversed.

As shown in Examples 1-5, Claude et al discloses the preparation of neotame by a process in which aspartame is reductively reacted with 3,3-dimethylbutyraldehyde in the presence of a platinum or palladium catalyst in a solvent which is a mixture of a 0.1 M aqueous solution of acetic acid and methanol. After the reaction is complete, the catalyst is removed by filtration, and the pH of the filtrate is adjusted to 5 by the addition of a few drops of a 1 N solution of sodium hydroxide. The methanol is "then removed under vacuum, the temperature being kept below 40°C," and a "white solid rapidly precipitates."

Thus, the process described in Claude et al differs from those which are presently claimed in a number of important ways. First, in the process of Claude et al acetic acid is added to the original reaction solvent and is not removed prior to the precipitation step. Even in the case when sodium hydroxide is added, acetate ions will remain in the solvent up to and

through the precipitation. In contrast, the crystallization in the presently claimed methods is carried out in a solvent which "is selected from the group consisting of water and mixtures of water and a lower alcohol" and which does not contain the fairly large concentration of acetic acid and/or acetate ions which is present in the solvent of Claude et al.

Moreover, the precipitation described in Claude et al does not involve carrying out the crystallization "such that the temperature of said solution is maintained above 30 °C until onset of nucleation of said N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine methyl ester." Instead, Claude et al merely discloses that the "temperature being kept below 40°C." Thus, Claude et al only states an upper temperature limit which was not exceeded and says nothing about any lower temperature limit. In fact, Claude et al never states any actual temperature, only that it is below 40°C. Just how much below 40°C is unstated.

Moreover, Claude et al does not even disclose what temperature is "kept below 40°C." It is evident that Examples 1-5 of Claude et al were carried out on a bench-top scale. Temperature control during the removal of methanol by evaporation under vacuum in such situations is typically achieved by placing the vessel in a water bath and monitoring-controlling the temperature of the water bath. Thus, one of skill in the art would understand that the Examples of Claude et al were carried out by maintaining the temperature of a water bath, not the filtrate itself, below 40°C.

Furthermore, as explained in detail below, the method of Claude et al does not yield A-type crystals.

For all of these reasons, the methods of Claims 5-11 are quite distinct from the procedure of Claude et al.

As for Claims 12-15, Applicants note that these claims recite the use of a specific type of seed crystals (A-type seed crystals). In sharp contrast, Claude et al not only is silent in regard to the use of any type of seed crystals, but also contains no disclosure of A-type crystals or method for preparing A-type crystals.

In support of these assertions, one of the present inventors, Mr. Kawahara, has carried out a substantial repetition of Example 1 of Claude et al and found that the method resulted in too low a yield of neotame, *i.e.*, a 50-60% yield. Mr. Kawahara then carried out another substantial repetition of Example 1 of Claude et al with the exception that the platinum catalyst was replaced by the palladium catalyst used in Example 2 of Claude et al, which also afforded a 50-60% yield.

Such low yields may be attributable to the use of acetic acid as part of the solvent for the hydrogenation reaction, as may be evidenced by U.S. Patent No. 5,728,862 (Prakash). In particular, the, Examiner's attention is directed to the different yields reported for Example 1 of Prakash in which no acetic acid was used and Comparative Example 1 of Prakash in which a 0.1M aqueous solution of acetic acid (60 ml) was used. As the Examiner will recognize, Comparative Example 1 of Prakash is a substantial repetition of Example 1 of Claude et al, with the exception that a palladium catalyst was used instead of the platinum catalyst and, thus, is a substantial repetition of Example 2 of Claude et al.

In any event, it must be noted that the crystals disclosed in Prakash, especially in Example 1 thereof, and in Claude et al, especially in Examples 1 and 2, are all B-type crystals (or their dried modification, G-type crystals). As described on page 2, line 17, through page 4, line 17 from the end, of the instant specification, the crystals of Example 1 of Prakash are B-type crystals. Moreover, Mr. Kawahara's substantial repetitions of Examples 1 and 2 of

Claude et al described above have revealed that the "white solid" rapidly precipitated in Examples 1 and 2 of Claude et al are also B-type crystals.

The formation of B-type crystals in the methods of Prakash and Claude et al may be attributed to excessively low nucleation temperatures.

The precipitation in Prakash was in fact carried out by stirring the aqueous/methanol solution at a temperature of 10 to 15°C for 2 to 12 hours as described in Example 1 of Prakash. See also column 3, line 66, through column 4, line 3, of Prakash, where the use of precipitation temperatures of 5 to 25 °C, most preferably about 10 to 15 °C, is disclosed. Such a low nucleation temperature of 10 to 15°C is far below the nucleation temperature of 30°C or greater recited in the present claims.

On the other hand, Example 1 of Claude et al indeed discloses that "The methanol is then removed by evaporation under vacuum, the temperature being kept below 40°C. A white solid rapidly precipitates." However, as explained above, it is obvious to those who are skilled in the art that the temperature which kept below 40°C is that of the water in the water bath, and not that of the content or mass in the vessel.

In fact, during his substantial repetitions of Examples 1 and 2 of Claude et al, Mr. Kawahara checked the temperature of the mass in the vessel often and found that the temperature of the mass inside the vessel was, in fact, about 23-28°C, which is below the nucleation temperature of 30°C or greater recited in the present claims. The temperature drop or difference between the bath (40°C) and the mass inside the vessel (about 23°C) is reasonably attributed to the heat of vaporization of the methanol.

For all of these reasons, the present claims are fully patentable over the teachings of Claude et al.

Tosoh indeed discloses the so-called seeding crystallization of Aspartame. However, Tosoh is completely silent in regard to the crystallization of neotame, the use A-type crystals of neotame as seed crystals, or even the existence of A-type crystals of neotame.

On page 5 of the Official Action, it is asserted that Aspartame "is very closely related in structure and properties to Neotame." It is then asserted that it would have been obvious to apply the seeding method of Tosoh to the crystallization of neotame. However, this logic is incorrect for the following reasons.

First, Applicants agree that Aspartame is somewhat related in structure to neotame. However, neotame is structurally similar to Aspartame only in the sense that neotame contains one Aspartame residue in addition to one 3,3-dimethylbutyl moiety. Therefore, if a chemical reaction involves some reaction site on an Aspartame molecule, neotame might behave like Aspartame in such a reaction. Thus, it might be said that neotame is related in certain chemical properties to Aspartame, only in this sense. Of course, in many chemical properties neotame and Aspartame react quite differently. For example, any reaction which relies on the presence of a $-NH_2$ group will not be possible with neotame.

Applicants also concede that Aspartame and neotame share, to a certain degree, the physiological property of imparting a sweet taste. However, the magnitude of this property is much greater for neotame.

However, Applicants submit that the process of crystallization is not related to the chemical reactivity of certain functional groups present in either Aspartame itself or the aspartame residue contained in neotame. Applicants further submit that crystallization is not a physiological property.

Instead, crystallization is a physical phenomenon, and at most a physico-chemical phenomenon. It is obvious and well known that the physical properties of neotame are quite distinct from those of Aspartame. For example the molecular weight of neotame is about 378 daltons, while that of Aspartame is only about 294 daltons. Moreover, neotame will have a vastly different shape as compared to Aspartame owing to the presence of the additional and relatively voluminous 3, 3-dimethylbutyl group.

When viewed from the perspective of physico-chemical properties, it is seen that the seeding crystallization of Aspartame does not suggest of the presently claimed seeding crystallization of neotame, because Neotame and Aspartame are quite different from each other in physical structure and therefore, in physical properties.

In fact, the different natures of Aspartame and neotame are supported by the disclosure of Tosoh itself. Thus, according to Tosoh, the seeding crystallization of Aspartame is for the purpose of obtaining Aspartame crystals having a larger width to length ratio, no polymorphism being involved therein (see Abstract on the front page of Tosoh). In sharp contrast, the presently claimed seeding crystallization is for the purpose of obtaining the same type, *i.e.*, A- type crystals of neotame as the seed crystals type.

If the assertions in the Official Action were correct, one would naturally expect that the presently claimed seeding crystallization would afford neotame crystals having a larger width to length ratio. This is, however, definitely not the case.

In any event, even if one were to combine the teachings of Tosoh with those of Claude et al, one would still not arrive at the presently claimed seeding method. As noted above, Claude et al contains no disclosure of A-type crystals of neotame or a method of making A-type crystals of neotame. Certainly, there is no disclosure of A-type crystals of neotame in

Tosoh. Thus, even if the teaching of these two references were combined, at most one would arrive at a process in which B-type crystals of neotame were used as the seed crystals.

In sharp contrast, present Claims 12-15 explicitly recite the use of seed crystals which "exhibit at least the following diffraction peaks as measured by x-ray diffraction, 2θ CuKα: a peak at 6.0°; a peak at 24.8°; a peak at 8.2°; and a peak at 16.5°," *i.e.*, A-type crystals.

For these reasons, the rejection should be withdrawn.

The rejections of the claims under 35 U.S.C. § 112, second paragraph, have been obviated by appropriate amendment. As the Examiner will note, Applicants have rewritten the claims such that they are free of the criticisms outlined on pages 2 and 3 of the Official Action. Applicants expressly state that these amendments are not narrowing and are solely for clarification. Again, the rejections should be withdrawn.

The objection to the specification has also been obviated by appropriate amendment. Specifically, Applicants have amended page 1 of the specification as suggested by the Examiner. Accordingly, the objection should be withdrawn.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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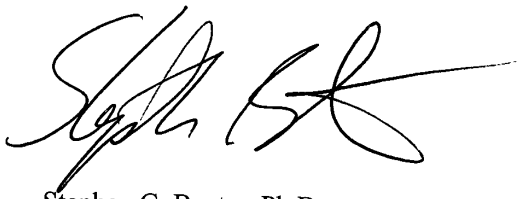

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IN THE SPECIFICATION

Page 1, after the title, please insert the following new paragraph:

--This application is a 371 of PCT/JP99/06082 filed on November 1, 1999, which claims the benefit of JP 310225 and JP 310226 both filed on October 30, 1998.--

IN THE CLAIMS

Please cancel Claims 1-4, without prejudice toward the further prosecution of these claims in a Continuation and/or Divisional Application.

Please add the following new Claims:

--5. (New) to 15. (New)--